

Second Supplemental Amendment for Application No. 09/623,068. Applicant(s) MCGINNIS ET AL. 2/5
August 2, 2004 submitted by fax to 1-703-872-9306

In the Specification

Please add the following new paragraph after the last (sixth) paragraph that was requested to be added to the Specification in the Supplemental Amendment 7/20/04 that begins with the words "The extension of the Risch & Merikangas analysis to include these more common, less optimal situations is illustrated", but before the heading "**Industrial Applicability**" that was formerly on page 4/ line 30 of the PCI application.

The inventor's calculations indicate that the power of the TDT and other association-based linkage tests is not markedly diminished or dramatically weakened as soon as the m/p ratio departs from unity and, or δ is not close to δ_{\max} as indicated by Muller-Myshok and Abel. The TDT and other association-based tests have increased power due to similarity of allele frequencies m and p, in more common, typical situations even when the ratio m/p departs significantly from unity and, or δ is not close to δ_{\max} . And it is practical to use this increased power in association-based linkage studies to detect evidence for linkage. When $r = 2$ linkage is virtually undetectable by χ^2_{asp} since ASP power is 0.10 or lower; by contrast the TDT is able to detect linkage but TDT power exceeds 0.50 only when δ is close to δ_{\max} and allele frequencies (m, p) are similar in magnitude. For $r = 4$, TDT power is substantially higher and, for most markers, exceeds 0.95 when $\delta = \delta_{\max}$ and exceeds 0.50 when $\delta = 1/2 \delta_{\max}$ thus indicating that when $r = 4$, the TDT could demonstrate linkage to many disease loci. For $r = 10$, TDT power is reasonably high (e.g., ≥ 0.66) when $\delta \geq 1/2 \delta_{\max}$. The choice of covering markers in versions of the invention is made with attention to (or based on) using similarity of allele frequencies (e.g., m and p) to increase the power (or achieve increased power) of an association-based linkage test to detect evidence for linkage. (See pp. 4, 5, 6 and 7 of the Background, the inventor's paper Ann. Hum. Genet. v. 62 p. 166 which also includes observations for $r = \infty$, p. 168 and Tables 1, 2 and 3 on pp. 165, 167 of the paper.)